PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61M 11/00, 15/00, 16/00

A1

(11) International Publication Number: WO 96/32149

(43) International Publication Date: 17 October 1996 (17.10.96)

(21) International Application Number: PCT/US96/05070

(22) International Filing Date: 12 April 1996 (12.04.96)

(30) Priority Data:
08/423,515 14 April 1995 (14.04.95) US

(71) Applicant: INHALE THERAPEUTIC SYSTEMS [US/US]; 1001 East Meadow Circle, Palo Alto, CA 94303 (US).

(72) Inventors: PLATZ, Robert, M.; 324 Valdez Avenue, Half Moon Bay, CA 94019 (US). PLATTON, John, S.; 330 Emerald Avenue, San Carlos, CA 94070 (US). FOSTER, Linda; 733 Carolina Avenue, Sunnyvale, CA 94086 (US). ELJAMAL, Mohammed; 1255 Saratoga Avenue, 206B, San Jose, CA 95129 (US).

(74) Agents: HESLIN, James, M. et al.; Townsend and Townsend and Crew, Steuart Street Tower, 20th floor, One Market Plaza, San Francisco, CA 94105 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: PULMONARY DELIVERY OF AEROSOLIZED MEDICAMENTS

(57) Abstract

According to the subject invention, dispersible dry powder pharmaceutical-based compositions are provided, including methods for their manufacture and dry powder dispersion devices. A dispersible dry power pharmaceutical-based composition is one having a moisture content of less than about 10 % by weight (%w) water, usually below about 5 %w and preferably less than about 3 %w; a particle size of about 1.0-5.0 μm mass median diameter (MMD), usually1.0-4.0 μm MMD, and preferably 1.0-3.0 μm MMD; a delivered dose of about >30 %, usually >40 %, preferably >50 %, and most preferred >60 %; and an aerosol particle size distribution of about 1.0-5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5-4.5 μm MMAD, and preferably 1.5-4.0 μm MMAD. Such compositions are of pharmaceutical grade purity.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia
AT	Austria
AU	Australia
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Côte d'Ivoire
CM	Cameroon
CN	China
CS	Czechoslovakia
CZ	Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GN	Guinea
GR	Greece
HU	Hungary
IE	Ireland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgystan
KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakia
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TT	Trinidad and Tobago
UA	Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Viet Nam

PULMONARY DELIVERY OF AEROSOLIZED MEDICAMENTS

BACKGROUND OF THE INVENTION

1. Field of the Invention.

The present invention relates generally to methods and compositions for the dry powder formulation of pharmaceuticals, including macromolecules, for pulmonary delivery.

Over the years, certain drugs have been sold in compositions suitable for forming a drug dispersion for oral inhalation (pulmonary delivery) to treat various conditions in humans. Such pulmonary drug delivery compositions are designed to be delivered by inhalation by the patient of a drug dispersion so that the active drug within the dispersion can reach the lung. It has been found that certain drugs delivered to the lung are readily absorbed through the alveolar region directly into blood circulation. Pulmonary delivery is particularly promising for the delivery of macromolecules (proteins, polypeptides and nucleic acids) which are difficult to deliver by other routes of administration. Such pulmonary delivery can be effective both for systemic delivery and for localized delivery to treat diseases of the lungs.

Pulmonary drug delivery can itself be achieved by different approaches, including liquid nebulizers, aerosol-based metered dose inhalers (MDI's), and dry powder dispersion devices. Aerosol-based MDI's are losing favor because they rely on the use of chlorofluorocarbons (CFC's), which are being banned because of their adverse effect on the ozone layer. Dry powder dispersion devices, which do not rely on CFC aerosol technology, are promising for delivering drugs

that may be readily formulated as dry powders. Many otherwise labile macromolecules may be stably stored as lyophilized or spray-dried powders by themselves or in combination with suitable powder carriers. The ability to deliver pharmaceutical compositions as dry powders, however, is problematic in certain respects. The dosage of many pharmaceutical compositions is often critical so it is necessary that any dry powder delivery system be able to accurately, precisely, and reliably deliver the intended amount of drug. Moreover, many pharmaceutical compositions are quite expensive. Thus, the ability to efficiently deliver the dry powders with a minimal loss of drug is critical. It is also essential that the powder be readily dispersible prior to inhalation by the patient in order to assure adequate distribution and systemic absorption.

A particularly promising approach for the pulmonary delivery of dry powder drugs utilizes a hand-held device with a hand pump for providing a source of pressurized gas. The pressurized gas is abruptly released through a powder dispersion device, such as a venturi nozzle, and the dispersed powder made available for patient inhalation. While advantageous in many respects, such hand-held devices are problematic in a number of other respects. The particles being delivered are less than 10 μm in size, usually in the range from 1μm to 5μm, making powder handling and dispersion more difficult than with larger particles. The problems are exacerbated by the relatively small volumes of pressurized gas, which are available using hand-actuated pumps. In particular, venturi dispersion devices are unsuitable for difficult-to-disperse powders when only small volumes of pressurized gas are available. Another requirement for hand-held and other powder delivery devices is efficiency. It is important that the concentration of drug in the bolus of gas be relatively high to reduce the number of breaths required to achieve a total dosage. The ability to achieve both adequate dispersion and small dispersed volumes is a significant technical challenge that requires in part that

each unit dosage of the powdered composition be readily and reliably dispersible.

SUMMARY OF THE INVENTION

According to the subject invention, dispersible dry powder pharmaceutical-based compositions are provided, including methods for their manufacture and dry powder dispersion devices. A dispersible dry powder pharmaceutical-based composition is one having a moisture content of less than about 10% by weight (%w) water, usually below about 5%w and preferably less than about 3%w; a particle size of about 1.0-5.0 μm mass median diameter (MMD), usually 1.0-4.0 μm MMD, and preferably 1.0-3.0 μm MMD; a delivered dose of about >30%, usually >40%, preferably >50%, and most preferred >60%; and an aerosol particle size distribution of about 1.0-5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5-4.5 μm MMAD, and preferably 1.5-4.0 μm MMAD. Such compositions are of pharmaceutical grade purity.

DESCRIPTION OF SPECIFIC EMBODIMENTS

The present invention is based at least in part on the dispersibility characteristics of the pharmaceutical-based dry powder compositions produced according to the present invention. The dispersibility characteristics of the subject pharmaceutical-based compositions means that they are more suitable for use in pulmonary delivery devices than compositions prepared by other methods. The compositions of the invention are readily aerosolized and rapidly absorbed through the lungs of a host when delivered by a dry powder inhaler.

DEFINITIONS

In interpreting the claims to the various aspects of this invention, there are several important definitions that should be considered.

The term "dispersibility" or "dispersible" means a dry powder having a moisture content of less than about 10% by weight (%w) water, usually below about 5%w and preferably less

than about 3%w; a particle size of about 1.0-5.0 μm mass median diameter (MMD), usually 1.0-4.0 μm MMD, and preferably 1.0-3.0 μm MMD; a delivered dose of about >30%, usually >40%, preferably >50%, and most preferred >60%; and an aerosol particle size distribution of about 1.0-5.0 μm mass median aerodynamic diameter (MMAD), usually 1.5-4.5 μm MMAD, and preferably 1.5-4.0 μm MMAD.

The term "powder" means a composition that consists of finely dispersed solid particles that are free flowing and capable of being readily dispersed in an inhalation device and subsequently inhaled by a subject so that the particles reach the lungs to permit penetration into the alveoli. Thus, the powder is said to be "respirable." Preferably the average particle size is less than about 10 microns (μm) in diameter with a relatively uniform spheroidal shape distribution. More preferably the diameter is less than about 7.5 μm and most preferably less than about 5.0 μm. Usually the particle size distribution is between about 0.1 μm and about 5 μm in diameter, particularly about 0.3 μm to about 5 μm.

The term "dry" means that the composition has a moisture content such that the particles are readily dispersible in an inhalation device to form an aerosol. This moisture content is generally below about 10% by weight (%w) water, usually below about 5%w and preferably less than about 3%w.

The term "therapeutically effective amount" is the amount present in the composition that is needed to provide the desired level of drug in the subject to be treated to give the anticipated physiological response. This amount is determined for each drug on a case-by-case basis. Guidelines are given hereafter.

The term "physiologically effective amount" is that amount delivered to a subject to give the desired palliative or curative effect. This amount is specific for each drug and its ultimate approved dosage level. Guidelines are given hereafter.

The term "pharmaceutically acceptable carrier" means that the carrier can be taken into the lungs with no significant adverse toxicological effects on the lungs.

COMPOSITIONS OF THE INVENTION

One aspect of this invention is a dispersible pharmaceutical-based dry powder composition for pulmonary delivery, the composition comprising a therapeutically effective amount of a pharmaceutical in combination with a pharmaceutically acceptable carrier.

In general, the compositions of this invention have a suitable for pulmonary delivery because of their dispersibility characteristics. Such compositions were not previously known in the art. In the dry state, the pharmaceutical may be in crystalline or amorphous form. Some examples of pharmaceutical compositions suitable for formulation into dispersible dry powders are listed in Table 1. These include macromolecule and non-macromolecule-based pharmaceuticals, usually macromolecules, with insulin, interleukin-1 receptor, parathyroid hormone (PTH-34), alpha-1 antitrypsin, calcitonin, low molecular weight heparin, heparin, interferon, and nucleic acids being preferred.

A therapeutically effective amount of active pharmaceutical will vary in the composition depending on the biological activity of the drug employed and the amount needed in a unit dosage form. Because the subject compounds are dispersible, it is highly preferred that they be manufactured in a unit dosage form in a manner that allows for ready manipulation by the formulator and by the consumer. This generally means that a unit dosage will be between about 0.5 mg and 15 mg of total material in the dry powder composition, preferably between about 2 mg and 10 mg. Generally, the amount of drug in the composition will vary from about 0.05%w to about 99.0%w. Most preferably the composition will be about 0.2% to about 97.0%w drug.

The amount of the pharmaceutically acceptable carrier is that amount needed to provide the necessary stability, dispersibility, consistency and bulking

characteristics to ensure a uniform pulmonary delivery of the composition to a subject in need thereof. Numerically the amount may be from about 0.05%w to about 99.95%w, depending on the activity of the drug being employed. Preferably about 5%w to about 95%w will be used.

The carrier may be one or a combination of two or more pharmaceutical excipients, but will generally be substantially free of any "penetration enhancers." Penetration enhancers are surface active compounds which promote penetration of a drug through a mucosal membrane or lining and are proposed for use in intranasal, intrarectal, and intravaginal drug formulations. Exemplary penetration enhancers include bile salts, e.g., taurocholate, glycocholate, and deoxycholate; fusidates, e.g., taurodehydrofusidate; and biocompatible detergents, e.g., Tweens, Laureth-9, and the like. The use of penetration enhancers in formulations for the lungs, however, is generally undesirable because the epithelial blood barrier in the lung can be adversely affected by such surface active compounds. The dry powder compositions of the present invention are readily absorbed in the lungs without the need to employ penetration enhancers.

The types of pharmaceutical excipients that are useful as carriers in this invention include stabilizers such as human serum albumin (HSA), bulking agents such as carbohydrates, amino acids and polypeptides; pH adjusters or buffers; salts such as sodium chloride; and the like. These carriers may be in a crystalline or amorphous form or may be a mixture of the two.

It has been found that HSA is particularly valuable as a carrier in that it provides improved dispersibility.

Bulking agents that are particularly valuable include compatible carbohydrates, polypeptides, amino acids or combinations thereof. Suitable carbohydrates include monosaccharides such as galactose, D-mannose, sorbose, and the like; disaccharides, such as lactose, trehalose, and the like; cyclodextrins, such as 2-hydroxypropyl-β-cyclodextrin; and polysaccharides, such as raffinose, maltodextrins, dextrans,

and the like; alditols, such as mannitol, xylitol, and the like. A preferred group of carbohydrates includes lactose, trehalose, raffinose maltodextrins, and mannitol. Suitable polypeptides include aspartame. Amino acids include alanine and glycine, with glycine being preferred.

Additives, which are minor components of the composition of this invention, may be included for conformational stability during spray drying and for improving dispersibility of the powder. These additives include hydrophobic amino acids such as tryptophan, tyrosine, leucine, phenylalanine, and the like.

Suitable pH adjusters or buffers include organic salts prepared from organic acids and bases, such as sodium citrate, sodium ascorbate, and the like; sodium citrate is preferred.

The unit dosage form, method of treatment, and process of preparation of this invention are described hereafter.

Unit Dosage Form.

Another aspect of this invention is a unit dosage form for pulmonary delivery of dispersible dry powder pharmaceutical-based compositions, which dosage form comprises a unit dosage receptacle containing a pharmaceutical-based dry powder composition, which composition comprises a therapeutically effective amount of a pharmaceutical in combination with a pharmaceutically acceptable carrier.

In this aspect of the invention, the composition of this invention (as discussed hereinbefore) is placed within a suitable dosage receptacle in an amount sufficient to provide a subject with drug for a unit dosage treatment. The dosage receptacle is one that fits within a suitable inhalation device to allow for the aerosolization of the interferon-based dry powder composition by dispersion into a gas stream to form an aerosol and then capturing the aerosol so produced in a chamber having a mouthpiece attached for subsequent inhalation by a subject in need of treatment. Such a dosage receptacle includes any container enclosing the composition known in the

art such as gelatin or plastic capsules with a removable portion that allows a stream of gas (e.g., air) to be directed into the container to disperse the dry powder composition. Such containers are exemplified by those shown in U.S. Patents 4,227,522 issued October 14, 1980; 4,192,309 issued March 11, 1980; and 4,105,027 issued August 8, 1978. Suitable containers also include those used in conjunction with Glaxo's Ventolin Rotohaler brand powder inhaler or Fison's Spinhaler brand powder inhaler. Another suitable unit-dose container which provides a superior moisture barrier is formed from an aluminum foil plastic laminate. The pharmaceutical-based powder is filled by weight or by volume into the depression in the formable foil and hermetically sealed with a covering foil-plastic laminate. Such a container for use with a powder inhalation device is described in U.S. Patent 4,778,054 and is used with Glaxo's Diskhaler® (U.S. Patents 4,627,432; 4,811,731; and 5,035,237). All of these references are incorporated herein by reference.

Method of Treating a Disease State.

Another aspect of this invention is a method of treating a condition responsive to treatment by a pharmaceutical of interest, which method comprises pulmonarily administering to a subject in need thereof a physiologically effective amount of a dispersible pharmaceutical-based dry powder composition that comprises a therapeutically effective amount of drug in combination with a pharmaceutically acceptable carrier.

Conditions that may be treated by the compositions of this are described in Table 1.

The physiologically effective amount needed to treat a particular condition or disease state will depend on the individual, the condition, length of treatment, the regularity of treatment, the type of drug, and other factors, but can be determined by one of ordinary skill in the medicinal arts.

It is presently believed that the effective absorption by a host of dry powder composition according to the present invention results from a rapid dissolution in the

ultra-thin (<0.1 (m) fluid layer of the alveolar lining of the lung. The particles of the present invention thus have a mean size which is from 10 to 50 times larger than the lung fluid layer, making it unexpected that the particles are dissolved and the interferon systemically absorbed in a rapid manner for either local lung or systemic treatment. An understanding of the precise mechanism, however, is not necessary for practicing the present invention as described herein.

The aerosolized pharmaceutical-based dry powders of this invention are particularly useful in place of parenteral delivery. Thus, the methods and compositions of the present invention will be particularly valuable in chronic treatment protocols where a patient can self-medicate. The patient can achieve a desired dosage by inhaling an appropriate amount of drug, as just described. The efficiency of systemic delivery via the method as just described will typically be in the range from about 15% to 50%.

Method for Aerosolizing the Powder.

Still another aspect of this invention is a device and method for aerosolizing a pharmaceutical-based dry powder composition that comprises a therapeutically effective amount of drug in combination with a pharmaceutically acceptable carrier, which method comprises dispersing an amount of the dry powder composition in a gas stream to form an aerosol and capturing the aerosol in a chamber having a mouthpiece for subsequent inhalation by a patient.

A further detailed description of this method is found in pending U.S. Patent Application Serial Nos.: 07/910,048 and 08/207,472, both of which are incorporated herein by reference.

Preparing the Compositions.

Still another aspect of this invention is a method for preparing a dispersible pharmaceutical-based dry powder composition of this invention that comprises spray drying an aqueous mixture of the drug and a pharmaceutically acceptable

carrier under conditions to provide a respirable dry powder composition.

Spray drying is a process in which a homogeneous aqueous mixture of drug and the carrier is introduced via a nozzle (e.g., a two fluid nozzle), spinning disc or an equivalent device into a hot gas stream to atomize the solution to form fine droplets. The aqueous mixture may be a solution, suspension, slurry, or the like, but needs to be homogeneous to ensure uniform distribution of the components in the mixture and ultimately the powdered composition. Preferably the aqueous mixture is a solution. The solvent, generally water, rapidly evaporates from the droplets producing a fine dry powder having particles 1 to 5 μm in diameter. Surprisingly, the drug is not degraded when it is exposed to the hot drying gas, and the interferon powders can be prepared having sufficient purity for pharmaceutical use. An acceptable purity is defined as less than 5% degradation products and contaminates, preferably less than 3% and most preferably less than 1%.

The spray drying is done under conditions that result in substantially amorphous powder of homogeneous constitution having a particle size that is respirable, a low moisture content and flow characteristics that allow for ready aerosolization. Preferably the particle size of the resulting powder is such that more than about 98% of the mass is in particles having a diameter of about 10 μm or less with about 90% of the mass being in particles having a diameter less than 5 μm. Alternatively, about 95% of the mass will have particles with a diameter of less than 10 μm with about 80% of the mass of the particles having a diameter of less than 5 μm.

The solutions may then be sprayed dried in conventional spray drying equipment from commercial suppliers, such as Buchi, Niro, Yamato Chemical Co., Okawara Kakoki Co., and the like, resulting in a substantially amorphous particulate product.

For the spraying process, such spraying methods as rotary atomization, pressure atomization and two-fluid atomization can be used. Examples of the devices used in

these processes include "Parubisu [phonetic rendering] Mini-Spray GA-32" and "Parubisu Spray Drier DL-41", manufactured by Yamato Chemical Co., or "Spray Drier CL-8," "Spray Drier L-8," "Spray Drier FL-12," "Spray Drier FL-16" or "Spray Drier FL-20," manufactured by Okawara Kakoki Co., can be used for the method of spraying using rotary-disk atomizer.

While no special restrictions are placed on the nozzle of the atomizer used in the process of spraying, it is recommended to use a nozzle which can produce a spray-dry composition with a grain diameter suitable for nasal, pharyngeal or pulmonary administration. For example, nozzle types "1A," "1," "2A," "2," "3" and the like, manufactured by Yamato Chemical Co., can be used for the above-mentioned spray-drier, manufactured by the same company. In addition, disks type "MC-50," "MC-65" or "MC-85," manufactured by Okawara Kakoki Co., can be used as rotary disks of the spray-drier atomizer, manufactured by the same company.

While no particular restrictions are placed on the gas used to dry the sprayed material, it is recommended to use air, nitrogen gas or an inert gas. The temperature of the inlet of the gas used to dry the sprayed materials such that it does not cause heat deactivation of the sprayed material. The range of temperatures may vary between about 50°C to about 200°C, preferably between about 50°C and 100°C. The temperature of the outlet gas used to dry the sprayed material, may vary between about 0°C and about 150°, preferably between 0°C and 90°C, and even more preferably between 0°C and 60°C. The fact that inlet and outlet temperatures above about 55°C can be used is surprising in view of the fact that most macromolecule-based drugs deactivate at that temperature, with nearly complete deactivation occurring at about 70°C.

The dispersible pharmaceutical-based dry powders of the present invention may optionally be combined with pharmaceutical carriers or excipients which are suitable for respiratory and pulmonary administration. Such carriers may serve simply as bulking agents when it is desired to reduce the interferon concentration in the powder which is being

delivered to a patient, but may also serve to enhance the stability of the interferon compositions and to improve the dispersibility of the powder within a powder dispersion device in order to provide more efficient and reproducible delivery of the interferon and to improve handling characteristics of the interferon such as flowability and consistency to facilitate manufacturing and powder filling.

Such carrier materials may be combined with the drug prior to spray drying, i.e., by adding the carrier material to the purified bulk solution. In that way, the carrier particles will be formed simultaneously with the drug particles to produce a homogeneous powder. Alternatively, the carriers may be separately prepared in a dry powder form and combined with the dry powder drug by blending. The powder carriers will usually be crystalline (to avoid water absorption), but might in some cases be amorphous or mixtures of crystalline and amorphous. The size of the carrier particles may be selected to improve the flowability of the drug powder, typically being in the range from 25 μm to 100 μm. A preferred carrier material is crystalline lactose having a size in the above-stated range.

Alternatively, dry powder compositions may be prepared by other processes such as lyophilization and jet milling as disclosed in WO 91/16038.

TABLE 1

SELECTED MACROMOLECULE DRUGS FOR SYSTEMIC APPLICATIONS

DRUG	INDICATIONS
Calcitonin	Osteoporosis Prophylaxis Paget's Disease Hypercalcemia
Erthropoetin (EPO)	Anemia
Factor IX	Hemophilia B
Granulocyte Colony Stimulating Factor (G-CSF)	Neutropenia
Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)	Bone Marrow Engraftment/Transplant Failure
Growth Hormone	Short Stature Renal Failure
Heparin	Blood Clotting
Heparin (Low Molecular Weight)	Blood Clotting
Insulin	Type I and Type II Diabetes
Interferon Alpha	Hepatitis B and C Hairy Cell Leukemia Kaposi's Sarcoma
Interferon Beta	Multiple Sclerosis
Interferon Gamma	Chronic Granulomatous Disease
Interleukin-2	Renal Cancer
Luteinizing Hormone Releasing Hormone (LHRH)	Prostate Cancer Endometriosis
Somatostatin Analog	Gastrointestinal Cancers
Vasopressin Analog	Diabetes Insipidus Bed Wetting
Follicle Stimulating Hormone (FSH)	Fertility
Amylin	Type I Diabetes
Ciliary Neurotrophic Factor	Lou Gehrig's Disease
Growth Hormone Releasing Factor (GRF)	Short Stature
Insulin-Like Growth Factor	Osteoporosis Nutritional Support
Insulinotropin	Type II Diabetes
Interferon Beta	Hepatitis B and C
Interferon Gamma	Rheumatoid Arthritis
Interleukin-1 Receptor Antagonist	Rheumatoid Arthritis
Interleukin-3	Adjuvant to Chemotherapy
Interleukin-4	Immunodeficiency Disease
Interleukin-6	Thrombocytopenia

TABLE 1 - Continued

SELECTED MACROMOLECULE DRUGS FOR SYSTEMIC APPLICATIONS

DRUG	INDICATIONS
Macrophage Colony Stimulating Factor (M-CSF)	Fungal Disease Cancer Hypercholesterolemia
Nerve Growth Factor	Peripheral Neuropathies
Parathyroid Hormone	Osteoporosis
Somatostatin Analog	Refractory Diarrheas
Thymosin Alpha 1	Hepatitis B and C
IIb/IIIa Inhibitor	Unstable Angina
Alpha-1 Antitrypsin	Cystic Fibrosis
Anti-RSV Antibody	Respiratory Syncytial Virus
Cystic Fibrosis Transmembrane Regulator (CFTR) Gene	Cystic Fibrosis
Deoxyribonuclease (DNase)	Chronic Bronchitis
Heparin	Asthma
Bactericidal/Permeability Increasing Protein (BPI)	Adult Respiratory Distress Syndrome (ARDS)
Anti-CMV Antibody	Cytomegalovirus
Interleukin-1 Receptor	Asthma

SELECTED NON-MACROMOLECULE DRUGS FOR SYSTEMIC AND LOCAL LUNG APPLICATIONS

DRUG	INDICATIONS
Pentamidine isethiouate	Pneumocystis carini pneumonia
Albuterol sulfate	Bronchospasm
Metaproterenol sulfate Beclomethasone diprepionate Triamcinolone acetamide Budesonide acetonide Ipratropium bromide Flunisolide Cromolyn sodium	Bronchial asthma
Ergotamine Tartrate	Migraines

The following examples are offered by way of illustration and not limitation.

EXPERIMENTAL

According the subject invention, the following dispersible dry powder formulations were prepared as described. All compositions produced according to the present invention meet the strict specifications for content and purity required of pharmaceutical products.

EXAMPLE I

20.0% INSULIN FORMULATION FOR PULMONARY DELIVERY

A. Formulation.

Bulk crystalline human zinc insulin, was obtained from Eli Lilly and Company, Indianapolis, IN. A 20% insulin formulation was achieved by combining 1.5 mg insulin per 1.0 mL deionized water with 4.96 mg/mL USP mannitol and 1.04 mg/mL citrate buffer (sodium citrate dihydrate USP and citric acid monohydrate USP) for a total solids concentration of 7.5 mg/mL at pH 6.7 ± 0.3.

B. Spray Drying.

A dry powder of the 20% insulin formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	2-8°C
Inlet temperature	120-122°C
Feed rate	5.3 mL/min
Outlet temperature	80-81°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at < 80°C for about 10 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The above 20% insulin dry powder composition contained 66.1% mannitol and 13.9% citrate. The composition

was found to contain 1.1 to 2.0% moisture as measured by a columbic Karl Fischer method using a Mitsubishi CA-06 Moisture Meter.

The particle size distribution of the composition was measured by liquid centrifugal sedimentation in a Horiba CAPA-700 Particle Size Analyzer following dispersion of the powder on Sedisperse A-11 (Micrometrics, Norcross, GA) and was determined to be 1.3 μm to 1.5 μm MMD.

The delivered dose of the insulin powder composition was measured by collecting the aerosol powder produced by a dry powder dispersion device, similar to devices described in co-pending U.S. Application Serial Numbers 07/910,048; 08/313,707; 08/309,691 and PCT/US92/05621, the disclosures of which are hereby incorporated by reference, on a filter placed over the device mouthpiece. The delivered dose of the insulin powder composition was determined to be 563 ± 16 μg or 60 to 64% of the total powder (5.0 mg) loaded into the device.

The aerosol particle size distribution, measured using a cascade impactor (California Measurements IMPAQ-6), was determined to be 2.0 μm MMAD, with 86% to 90% of the particles < 5.0 μm in diameter.

The insulin content of the powder, measured by reverse phase HPLC (rpHPLC) was determined to be 197 μg/mg powder, accounting for 99% of the expected insulin. No degradation peaks were detected in the chromatogram.

EXAMPLE II

5.0% PARATHYROID HORMONE FORMULATION FOR PULMONARY DELIVERY

A. Formulation.

Bulk 34 amino acid active fragment of parathyroid hormone, PTH (1-34), was obtained from BACHEM CALIFORNIA, Torrance, CA. A 5.0% PTH (1-34) formulation was achieved by combining 0.375 mg PTH (1-34) per 1.0 mL deionized water with 6.06 mg/mL mannitol USP and 1.04 mg/mL citrate buffer (sodium citrate dihydrate USP and citric acid monohydrate USP) for a total solids concentration of 7.48 mg/mL at pH 6.3.

B. Spray Drying.

A dry powder of the 5.0% PTH (1-34) formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	2-8°C
Inlet temperature	122-124°C
Feed rate	5.2 mL/min
Outlet temperature	73-74°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at < 80°C for about 5 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above 5.0% PTH (1-34) dry powder composition contained 81.0% mannitol and 13.9% citrate. The formulation contained 0.5% moisture.

The particle size distribution of the composition was determined to be 2.4 μm and 2.7 μm MMD in separate measurements.

The delivered dose of the PTH (1-34) powder was determined to be 161 μg or 64.5% and 175 μg or 69.2% in separate measurements.

The PTH (1-34) content of the powder, measured by rpHPLC was determined to be 48.5 μg/mg powder, accounting for 97% of the expected value. No degradation peaks were detected in the chromatogram.

EXAMPLE III

0.7% INTERLEUKIN-1 RECEPTOR FORMULATION FOR PULMONARY DELIVERY

A. Formulation.

Bulk interleukin-1 receptor, IL-1 receptor, was obtained from Immunex Corporation, Seattle, WA. A 0.7% IL-1 receptor formulation was achieved by combining 0.053 mg IL-1 receptor per 1.0 mL deionized water with 7.07 mg/mL raffinose (Pfanstiehl, Waukegan, IL) and 0.373 mg/mL Tris buffer at pH 7.18.

B. Spray Drying.

A dry powder of the 0.7% IL-1 receptor formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	2-8°C
Inlet temperature	135-137°C
Feed rate	4.9 mL/min
Outlet temperature	92-93°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at 90°C for about 15 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above 0.7% IL-1 receptor dry powder composition contained 94.3% raffinose and 5.0% Tris. The formulation contained 1.84 ± 0.25% moisture.

The particle size distribution of the composition was determined to be 1.95 μm MMD with 100% of the particles < 5.0 μm.

The delivered dose of the IL-1 receptor powder was determined to be 22.3 ± 2.0 μg or 53.4 ± 4.7%.

The aerosol particle size distribution, was determined to be 3.2 μm MMAD, with 77% of the particles < 5.0 μm in diameter.

The IL-1 receptor content of the powder as measured by rpHPLC was determined to be 8.4 μg/mg, accounting for 120% of the expected IL-1 receptor. No degradation peaks were detected in the chromatogram.

EXAMPLE IV

5.0% INTERLEUKIN-1 RECEPTOR FORMULATION FOR PULMONARY DELIVERY

A. Formulation.

Bulk interleukin-1 receptor, IL-1 receptor, was obtained from Immunex Corporation, Seattle, WA. A 5.0% IL-1 receptor formulation was achieved by combining 0.375 mg IL-1 receptor per 1.0 mL deionized water with 6.77 mg/mL raffinose and 0.351 mg/mL Tris buffer at pH 7.35.

B. Spray Drying.

A dry powder of the 5.0% IL-1 receptor formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	2-8°C
Inlet temperature	138°C
Feed rate	4.9 mL/min
Outlet temperature	91°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at 90°C for about 15 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above 5.0% IL-1 receptor dry powder composition contained 90.3% raffinose and 4.7% Tris. The formulation contained 1.75 ± 0.26% moisture.

The particle size distribution of the composition was determined to be 2.74 μm MMD with 97% of the particles < 5.0 μm.

The delivered dose of the IL-1 receptor powder was determined to be 123.4 ± 24.5 μg or 49.3 ± 9.8%.

The aerosol particle size distribution, was determined to be 4.1 μm MMAD, with 64% of the particles < 5.0 μm in diameter.

The IL-1 receptor content of the powder as measured by rpHPLC was determined to be 52.7 ± 1.8 μg/mg, accounting for 105% of the expected IL-1 receptor. No degradation peaks were detected in the chromatogram.

EXAMPLE V

26.7% HUMAN CALCITONIN FORMULATION FOR PULMONARY DELIVERY

A. Formulation.

Bulk human calcitonin was obtained from Ciba-Geigy. A 26.7% human calcitonin formulation was achieved by combining 1.9 mg human calcitonin per 1.0 mL deionized water with 4.3 mg/mL mannitol and 0.9 mg/mL citrate buffer at pH 3.85.

B. Spray Drying.

A dry powder of the 26.7% human calcitonin formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	4°C
Inlet temperature	119°C
Feed rate	5.5 mL/min
Outlet temperature	78°C
Atomizer coolant temperature	0-5°C
Cyclone coolant temperature	25-30°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at 80°C for about 10 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above 26.7% human calcitonin dry powder composition contained 60% mannitol and 13.3% citrate. The formulation contained 0.71% moisture.

The particle size distribution of the composition was determined to be 1.33 ± 0.63 μm MMD.

The delivered dose of the human calcitonin powder was determined to be 76.8 ± 6.7%.

The human calcitonin content of the powder as measured by rpHPLC was determined to be 272.0 μg/mg, accounting for 102 ± 1.7% of the expected human calcitonin. No degradation peaks were detected in the chromatogram.

EXAMPLE VI

90% ALPHA-1 ANTITRYPSIN FORMULATION FOR PULMONARY DELIVERY

A. Formulation.

Bulk alpha-1 antitrypsin, A1A, was obtained from Armour Pharmaceutical Company, Kankakee, IL. A 90% A1A formulation was achieved by combining 4.89 mg A1A per 1.0 mL deionized water with 0.54 mg/mL citrate buffer at pH 6.0.

B. Spray Drying.

A dry powder of the 90% A1A formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	4°C
Inlet temperature	98-101°C
Feed rate	5.0 mL/min

Outlet temperature	65°C
Atomizer coolant temperature	2-8°C
Cyclone coolant temperature	30°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at 69°C for about 10 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above 90% A1A dry powder composition contained 10.0% citrate. The formulation contained 4.79% moisture.

The particle size distribution of the composition was determined to be 1.71 ± 0.87 μm MMD.

The delivered dose of the 90% A1A powder was determined to be 67.0 ± 5.0%.

The aerosol particle size distribution, was determined to be 1.0 μm MMAD, with 90% of the particles < 5.0 μm in diameter.

The A1A content of the powder as measured by rpHPLC was determined to be 80% of the expected value. No degradation peaks were detected in the chromatogram. The activity after spray drying was determined to be 74 ± 1%

EXAMPLE VII

0.3% BETA INTERFERON FORMULATION FOR PULMONARY DELIVERY CONTAINING HUMAN SERUM ALBUMIN

A. Formulation.

Bulk beta interferon, IFN-β, was obtained from Toray Industries, Inc., Tokyo, Japan. A 0.3% IFN-β formulation was achieved by combining 0.025 mg IFN-β per 1.0 mL deionized water with 5.54 mg/mL human serum albumin (HSA), 2.3 mg/mL citrate buffer and 0.345 mg/mL of NaCl at pH 4.5.

B. Spray Drying.

A dry powder of the 0.3% IFN-β formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	2-8°C
Inlet temperature	93°C
Feed rate	2.7 mL/min
Outlet temperature	62°C

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above 0.3% IFN-β dry powder composition contained 66.0% HSA, 27.4% citrate, 4.1% NaCl. The formulation contained 4.22% moisture.

The particle size distribution of the composition was determined to be 1.62 μm MMD with 94.8% of the particles < 5 μm.

The delivered dose of the 0.3% IFN-β powder was determined to be 9.9 μg/mg or 66.0 ± 4.0%.

The aerosol particle size distribution, was determined to be 2.0 μm MMAD, with 85% of the particles < 5.0 μm in diameter.

The IFN-β activity of the powder as measured by IFN-β enzyme immunoassay (Toray-Fuji Bionics) and was determined to be 109 ± 8% of the expected activity.

EXAMPLE VIII

0.3% BETA INTERFERON FORMULATION FOR PULMONARY DELIVERY CONTAINING RAFFINOSE

A. Formulation.

Bulk beta interferon, IFN-β, was obtained from Toray Industries, Inc., Tokyo, Japan. A 0.3% IFN-β formulation was achieved by combining 0.025 mg IFN-β per 1.0 mL deionized water with 4.7 mg/mL raffinose, 1.0 mg/mL human serum albumin

(HSA), 2.3 mg/mL citrate buffer and 0.3 mg/mL of NaCl at pH 4.5.

B. Spray Drying.

A dry powder of the 0.3% IFN-β formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	2-8°C
Inlet temperature	145°C
Feed rate	5.0 mL/min
Outlet temperature	87°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at 97°C for about 5 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above 0.3% IFN-β dry powder composition contained 56.4% raffinose, 11.9% HSA, 27.4% citrate, 3.5% NaCl. The formulation contained 0.69% moisture.

The particle size distribution of the composition was determined to be 2.06 μm MMD with 88.9% of the particles < 5 μm.

The delivered dose of the 0.3% IFN-β powder was determined to be 10.2 μg/mg or 68.0 ± 2.0%.

The aerosol particle size distribution, was determined to be 2.5 μm MMAD, with 84% of the particles < 5.0 μm in diameter.

The IFN-β activity of the powder as measured by IFN-β enzyme immunoassay (Toray-Fuji Bionics) and was determined to be 109 ± 8% of the expected activity.

EXAMPLE IX

93% LOW MOLECULAR WEIGHT HEPARIN FORMULATION FOR PULMONARY DELIVERY

A. Formulation.

Bulk low molecular weight heparin sodium salt (Av. Mol. Wt.: Approx. 6000) from porcine intestinal mucosa, heparin (LMW), was obtained from Sigma Chemical, St. Louis, MO.. A 93% heparin (LMW) formulation was achieved by combining 6.9 mg heparin (LMW) per 1.0 mL deionized water with 0.5 mg/mL HSA at pH 6.9.

B. Spray Drying.

A dry powder of the 93% heparin (LMW) formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	2-8°C
Inlet temperature	140°C
Feed rate	3.8 mL/min
Outlet temperature	85°C
Atomizer coolant temperature	2-8°C
Cyclone coolant temperature	20°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at 80°C for about 10 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above 93% heparin (LMW) dry powder composition contained 7.0% HSA.

The delivered dose of the 93% heparin (LMW) powder was determined to be 60.0 ± 1.0%.

The aerosol particle size distribution, was determined to be 3.5 μm MMAD, with 70% of the particles < 5.0 μm in diameter.

EXAMPLE X

97% UNFRACTIONATED HEPARIN FORMULATION FOR PULMONARY DELIVERY

A. Formulation.

Bulk unfractionated heparin sodium salt from porcine intestinal mucosa, heparin, was obtained from Sigma Chemical, St. Louis, MO. A 97% heparin formulation was achieved by combining 7.0 mg heparin per 1.0 mL deionized water with 0.25 mg/mL HSA at pH 6.55.

B. Spray Drying.

A dry powder of the 97% heparin formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	2-8°C
Inlet temperature	150°C
Feed rate	4.0 mL/min
Outlet temperature	85°C
Atomizer coolant temperature	2-8°C
Cyclone coolant temperature	20°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at 80°C for about 10 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above 97% heparin dry powder composition contained 3.0% HSA. The formulation contained 5.11% moisture.

The particle size distribution of the composition was determined to be 2.0 to 2.5 μm MMD.

The delivered dose of the 97% heparin powder was determined to be 79.0 ± 6.0%.

The aerosol particle size distribution, was determined to be 3.2 μm MMAD, with 70% of the particles < 5.0 μm in diameter.

EXAMPLE XI

LIPID VECTOR GENE FORMULATION FOR PULMONARY DELIVERY

A. Formulation.

Bulk pCMVβ DNA:Lipid vector was obtained from Genzyme Corporation, Cambridge, MA. A 0.71% DNA:Lipid vector formulation was achieved by combining 0.005:0.03 mg DNA:Lipid vector per 1.0 mL deionized water with 5.3 mg/mL glycine (J.T. Baker) 0.3 mg/mL HSA at pH 6.4.

B. Spray Drying.

A dry powder of the DNA:Lipid vector formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	2-8°C
Inlet temperature	120°C
Feed rate	3.8 mL/min
Outlet temperature	71°C
Atomizer coolant temperature	2-8°C
Cyclone coolant temperature	2-8°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at 65°C for about 5 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above 0.71% DNA:Lipid vector dry powder composition contained 93.97% glycine, and 5.32% HSA.

The particle size distribution of the composition was determined to be 2.0 μm MMD.

The delivered dose of the 97% heparin (HMW) powder was determined to be 64.0 ± 1.0%.

The aerosol particle size distribution, was determined to be 2.4 μm MMAD, with 75% of the particles < 5.0 μm in diameter.

Activity after spray drying was determined to be 160% of the expected value.

EXAMPLE XII

ADENOVIRAL VECTOR GENE FORMULATION FOR PULMONARY DELIVERY

A. Formulation.

Bulk pCMVβ DNA:Adenovirous vector was obtained from Genzyme Corporation, Cambridge, MA. A DNA:adenovirous vector formulation was achieved by combining 108 PFU/mL DNA:Lipid vector per 1.0 mL deionized water with 6.1 mg/mL glycine J.T. Baker) 2.5 mg/mL HSA, 1.9 mg/mL phosphate buffer at pH 7.4.

B. Spray Drying.

A dry powder of the DNA:Lipid vector formulation described above was produced by spray drying the aqueous mixture using a Buchi Laboratory Spray Dryer under the following conditions:

Temperature of aqueous mixture	2-8°C
Inlet temperature	105°C
Feed rate	2.9 mL/min
Outlet temperature	72°C
Atomizer coolant temperature	2-8°C
Cyclone coolant temperature	20°C

Once the aqueous mixture was consumed, the outlet temperature was maintained at 70°C for about 10 minutes by slowly decreasing the inlet temperature to provide a secondary drying.

C. Characterization.

The following characterization of the dry powder formulation described above was carried out using the methods described in Example I unless indicated otherwise.

The above DNA:adenovirous vector dry powder composition contained 58% glycine, and 24% HSA and 18% phosphate buffer.

The particle size distribution of the composition was determined to be 2.3 μm MMD.

The delivered dose of the 97% heparin (HMW) powder was determined to be 51.0 ± 1.0%.

The aerosol particle size distribution, was determined to be 1.8 μm MMAD, with 80% of the particles < 5.0 μm in diameter.

Activity after spray drying was determined to be 76% of the expected value.

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

The invention now being fully described, it will be apparent to one of ordinary skill in the art that many changes and modifications can be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A dispersible pharmaceutical-based dry powder composition for pulmonary delivery, said composition comprising a therapeutically effective amount of a pharmaceutical in combination with a pharmaceutically acceptable carrier, wherein the composition comprises particles and wherein 95% of the mass of the composition comprises particles having a particle size below 10 μm.

2. A dispersible pharmaceutical-based dry powder composition for pulmonary delivery, said composition comprising a therapeutically effective amount of a macromolecule selected from the group consisting of interleukin 1 receptor, heparin, low molecular weight heparin, and calcitonin, in combination with pharmaceutically acceptable carrier.

3. The composition of claim 1 or 2, wherein the composition is substantially free from penetration enhancers.

4. The composition of claim 2 or 3, wherein the carrier comprises HSA.

5. The composition of claim 3 or 4, wherein the carrier further comprises a carbohydrate bulking agent.

6. The composition of claim 1 or 2, wherein about 95% of the mass of the dry powder composition has a particle size of less than 10 μm.

7. The composition of claim 1 or 6, wherein about 80% of the mass of the dry powder composition has a particle size of less than 5μm.

8. The composition of claim 1, wherein the pharmaceutical comprises a macromolecule selected from the group consisting of insulin, interleukin 1 receptor,

parathyroid hormone alpha-1 antitrypsin, calcitonin, low molecular weight heparin, and nucleic acids.

9. A unit dosage form for pulmonary delivery of a pharmaceutical, which dosage form comprises a unit dosage receptacle containing a dispersible pharmaceutical-based dry powder composition, which composition comprises a therapeutically effective amount of the pharmaceutical in combination with a pharmaceutically acceptable carrier according to any of claims 1-8.

10. A method of treating a disease state responsive to treatment by a pharmaceutical, which method comprises pulmonarily administering to a subject in need thereof a physiologically effective amount of a dispersible pharmaceutical-based dry powder composition according to any of claims 1-8.

11. A method for aerosolizing a pharmaceutical-based dry powder composition that comprises a therapeutically effective amount of the pharmaceutical in combination with a pharmaceutically acceptable carrier, which method comprises:

dispersing an amount of a dry powder composition according to any of claims 1-8 in a gas stream to form an aerosol and

capturing the aerosol in a chamber suitable for subsequent inhalation by a patient.

12. A method for preparing a spray-dried, pharmaceutical-based dry powder that comprises a therapeutically effective amount of a pharmaceutical and a pharmaceutically acceptable carrier, which method comprises spray drying an aqueous mixture of the pharmaceutical and the carrier under conditions to provide a respirable dry powder comprising particles wherein 95% of the mass of the composition comprises particles having a particle size below 10 μm.

13. A method for preparing a spray-dried pharmaceutical-based dry powder composition that comprises a therapeutically effective amount of a pharmaceutical and a pharmaceutically acceptable carrier, which method comprises spray drying an aqueous mixture of a pharmaceutical selected from the group consisting of parathyroid hormone, interleukin 1 receptor, heparin, low molecular weight heparin, and calcitonin.

14. The method of claim 12 or 13, wherein the carrier comprises HSA.

15. The method of claim 14, wherein the carrier further comprises a carbohydrate bulking agent.

16. The method of claim 15, wherein the bulking agent is mannitol.

17. The method of claim 12, wherein 80% of the mass of the spray-dry composition has a particle size less than 5 μm.

18. A spray-dried, macromolecule-based dry powder composition for pulmonary delivery, said composition comprising a therapeutically effective amount of the macromolecule in combination with a pharmaceutically acceptable carrier produced by the method of claims 12-17.

19. Compositions as in claims 1-8, having a moisture content below 10%.

INTERNATIONAL SEARCH REPORT

International application No. PCT/US96/05070

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61M 11/00, 15/00, 16/00
US CL :128/200.14, 203.12,.203.15
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/200.14, 203.12,.203.15

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, SEARCH TERMS: SPRAY DRY? OR DRIED, POWDER, LUNG, CALCITONIN, INSULIN, INHAL?, HEPARIN, ANTITRYPSIN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,260,306 (BOARDMAN ET AL.) 09 NOVEMBER 1993, SEE COLS.3-5.	1-19
Y	US, A, 5,384,133 (BOYES ET AL.) 24 JANUARY 1995, SEE COL.3, LINE 8; COL.4, LINES 17-20; COL.5, LINES 5,6; COL.9, LINES 49-COL.10, LINE 28.	2,8,13

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be part of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 AUGUST 1996	27 AUG 1996

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	FOR AARON J. LEWIS
Facsimile No. (703) 305-3230	Telephone No. (703) 308-0716

Form PCT/ISA/210 (second sheet)(July 1992)★